REMARKS/ARGUMENTS

Claims 13-16, 19, 20, and 24-26 are pending. No claims are added, amended, or canceled.

Replacement figures are submitted herewith. This submission is believed to remedy the alleged drawing informalities.

Claims 13-16, 19, 20, and 24-26 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. Although the Office Action acknowledges that the instant specification enables the use of the instant compositions as antisense agents in unicellular organisms and cells in culture (Office Action at page 2), the Office Action alleges that Applicant's claimed methods are not enabled for multicellular organisms. As discussed below, the available evidence demonstrates that practice of the claimed methods are, in fact, enabled.

The Office Action presents several journal articles in support of the allegation of lack of enablement. These articles are used to allege various problems in implementing antisense technology and to question whether antisense technology will even work *in vivo*. Applicant notes, however, that advances in science and technology typically encounter some level of skepticism. The magnitude of such skepticism is arguably proportional to the magnitude of the advance. In the final analysis, it is not relevant whether skeptics exist but, rather, whether they were right. Concerning the instant claims, the mere fact that a group of individuals have predicted that methods such as those claimed would not work is of no relevance to the enablement of the instant claims because there is clear evidence that such predictions were incorrect.

Clinical trials of antisense therapies have established that antisense technology does work in accordance with the principles and guidance set forth in the present application. Isis Pharmaceuticals has 11 clinical trials ongoing at the present time where the compound under investigation is an antisense compound. Furthermore, the antisense drug Fomivirsen, was approved for marketing by the FDA in 1998. Applicant further submits herewith a series of press releases dated September 10, 2003, December 9, 2003, February 6, 2004, April 20, 2004, and May 3, 2004 in which Genta Incorporated announced progress of its antisense drug Genasense™, including completion of Phase 3 clinical trials against malignant melanoma

(the press releases are also available online at http://www.genta.com). Although Genasense™ has not yet been approved for commercial sale in the treatment of malignant melanoma (see attached press release dated May 3, 2004), it is still in Phase 3 clinical trials for at least two indications. Thus, the available evidence shows that the skeptics who doubted whether antisense technology would work *in vivo* were wrong.

Further, the level of skepticism found in the cited art is less than presented in the arguments set forth in the Office Action. The Office Action, for example, neglects to mention passages in the cited art that could be used to argue a contrary position. The Rojanasakul reference, for example, states that compounds such as those recited in the claims show great promise:

> [s]everal ON drugs have already demonstrated enough promise to justify clinical trials. They are being tested in patients suffering from leukemia, AIDS, and other diseases in which improved treatments are necessary. It is expected that in the future these ON drugs will be commonly used to treat those diseases for which no effective therapies yet exist.

See, the Rojanasakul reference at page 126. This passage serves as compelling evidence that the state of the art of oligonucleotide therapeutics, at the time the present application was filed, was such that an artisan could readily obtain at least some measurable test results once armed with the teachings of the present application. As noted at page 7 of the Remand to the Examiner, this evidence is relevant to the patentability considerations. Indeed, references must be considered as a whole. *In re Keller*, 642 F.2d 413, 425 (C.C.P.A. 1981).

The Office Action mistakenly suggests that the factors to be considered in regard to enablement point to a lack of enablement. The Office Action (page 3) alleges that the quantity of experimentation would be high for one skilled in the art to practice the instant inventions. The Office Action further quotes from the Rojanasakul reference (page 118, column 1), "it should be pointed out that the *in vitro* effects of PNAs may not necessarily reflect their *in vivo* effects...." *Id.* As discussed above, it is now clear that antisense technology does work *in vivo*. This evidence, which is not addressed in the Office Action, makes it clear that the level of needed experimentation is considerably less than alleged. That some experimentation may be required to determine optimum parameters does not preclude

enablement so long as the amount of experimentation is not unduly extensive. *W. L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303, 316 (Fed. Cir. 1983). In light of the information presented herewith, Applicant contends that the disclosure is adequate and would not require undue experimentation to practice the instant inventions.

The Office Action (page 4) also alleges that the instant application does not provide proper guidance or direction for one skilled in the art to practice the claimed inventions. Applicant notes that the Examiner admits that the specification enables the use of the instant compositions as antisense agents in unicellular organisms and cells in culture (Office Action at page 2). In addition to the portions of the application cited in the Office Action (page 4) as providing guidance on the administration of antisense agents, utilization of the compounds of the instant invention in pharmaceutical compositions and their administration to multicell organisms is discussed on page 22, line 9 to page 24, line 27. Applicant submits that one skilled in the art, who is admittedly enabled to practice the technology on unicellular organisms armed with the aforementioned guidance, is enabled to practice the instantly claimed inventions on multicell organisms.

Also, the state of the prior art is clearer than the analysis on page 5 of the Office Action would indicate. Likewise, the predictability of the art is much higher than that which is argued in the Office Action. As discussed above, the skeptics have not been proven correct in this field. Successful clinical trials indicate that antisense technology is viable. Further, as discussed in the Remand to the Examiner at page 7, such evidence is relevant to the analysis of the predictability of the field.

Furthermore in regard to claims 20 and 24-26, the Office Action mistakenly asserts that "even though claims 20 and 24-26 do not recite a hybridization step, it is clear from the disclosure ....that these claims are construed as requiring hybridization of the PNA antisense agent(s)" (Office Action at page 6). Not only is such an allegation contrary to the plain meaning of the claim language, it is inconsistent with the Board's Remand to the Examiner, which acknowledges that claim 20 "only requires that the organism be contacted with a compound according to the claim" (Remand to the Examiner at page 8). One skilled in the art is clearly enabled to perform such a method. For at least this reason, Applicants submit that the rejection be withdrawn.

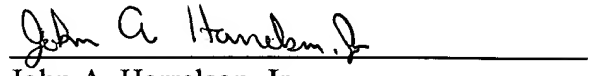
In addition, it is well known that pharmaceutical inventions encounter certain issues not found in all inventive fields. The mere existence of problems associated with the claimed inventions does not negate their patentablility. Rather, such problems are to be expected. It is well-established that pharmaceutical inventions usually require further research and development. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). Were such inventions not patentable long before being optimized or ready for human use, the incentive to fully research and develop vital drugs and potential cures would be completely removed. *Id.* at 1567-68.

In short, no disclosure other than that made by Applicant in the instant application was necessary for those skilled in the art to practice the inventions as presently claimed. This is the hallmark of enablement, and in no way is rebutted by the mere fact that there were those who doubted whether the underlying technology would ultimately be found to work. For these reasons and for those already of record which are hereby incorporated by reference, no clearer case of enablement can be shown. Accordingly, the rejection under 35 U.S.C. § 112, first paragraph, is improper and should be withdrawn.

The foregoing is believed to constitute a complete and full response to the Office Action of record. Accordingly, an early and favorable reconsideration of the rejections and an allowance of all of pending claims is earnestly solicited.

Respectfully submitted,

Date: May 18, 2004



John A. Harrelson, Jr.
Registration No. 42,637

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439